REMARKS

By this Amendment, Applicant has amended claims 40 to 45, without conceding the correctness of the Examiner's position and to expedite the prosecution of this application. Applicant notes that claims 1 to 39, and 50 were previously canceled. Applicant maintains that the amended claims are well supported by the specification and there is no issue of new matter. Accordingly, Applicant respectfully requests the entry of this Amendment. Upon entry, claims 40 to 49 will be pending and under examination.

Abstract

In Action Item 10 on page 3 of the Office Action, the Examiner requested that the Abstract be submitted on a separate sheet of paper. In response, Applicant is presenting the abstract not exceeding 150 words in a single paragraph on a separate sheet of paper.

Sequence Listing

In response to Action Item 11a on pages 3 and 4 of the Office Action, Applicant hereby resubmits a copy of the Sequence Listing in computer-readable form as required by 37 C.F.R. 1.821 (e), and the Statement to Comply With Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures (**Exhibit A,** 26 pages and a **floppy disk**).

Applicant hereby declares in the attached Statement that the information recorded in computer readable form is identical to the written Sequence Listing (**Exhibit B**) (1 page).

The attached Sequence Listing (**Exhibit A** and **floppy disk**) was created with PatentIn Version 3.3 and deemed free of errors by Checker 4.4.0.

Additionally, Applicant has amended the specification to insert Sequence ID Nos. to the Amino Acid sequences contained in the specification.

Applicant believes that the application is in compliance with all Sequence Listing requirements, and there is no issue of new matters.

Description of the Figures

In response to Action Item 11b on page 4 of the Office Action, Applicant has added description for Figures 10A and 10B.

Application Title

In accordance with the Examiner's suggestion in Action Item 11c on page 4 of the Office Action, Applicant has amended the title of the specification to clearly reflect the nature of the claimed subject matter.

Rejection under 35 U.S.C. 112, second paragraph

In response to Action Items 12a and 12b on pages 5 and 6 of the Office Action, but without conceding the correctness of the Examiner's position and to expedite the prosecution of this application, Applicant has amended claim 45 such that the term "derived" has been deleted and the substance of the claim is presented in more clarity. There is support for the idea of

introducing back-mutations into the framework-patched immunoglobulin throughout the specification, for examples, on page 16, lines 8-16, and on page 32, lines 9-16.

The Examiner also asks what the criteria are for the selection of which parent amino acid sequences to reinsert into the FR-patched immunoglobulin. Applicant would argue that one of skill in the art would know what criteria to use to perform such back-mutations and that the specification also provides adequate guidance on how to do so, for example, on page 2, lines 8-17 (where the disclosures of U.S. Pat. No. 5,585,089, U.S. Pat. No. 5,693,762, and U.S. Pat. No. 5,693,761 are incorporated by reference), and page 11, line 34 to page 12, line 5, where these same patents are incorporated by reference.

In response to Action Item 12c on pages 6 and 7 of the Office Action, and at the request of the Examiner, but without conceding the correctness of the Examiner's position and to expedite the prosecution of this application, Applicant has hereby amended claims 41 to 44 by eliminating the term "prior experience".

Accordingly, Applicant respectfully requests the reconsideration and withdrawal of this ground of rejection.

Rejection under 35 U.S.C. 103(a)

In Action Item 13 on pages 7 to 14 of the Office Action, the Examiner admits that "Queen et al. do not specifically teach a humanized or re-engineered antibody comprising FR's that are from different heavy chain variable regions and from different

light chain variable regions,...." However, the Applicant respectfully submits that the "deficiencies" of Queen et al. are not made up for in the teachings of Cohen et al and Benhar et al. Rather, the teachings of Cohen et al. and Benhar et al. confirm the uniqueness and novelty of the current invention for the reasons discussed below.

First, the Examiner asserts that Cohen et al. teach a humanized antibody wherein each FR is used to search for the most homologous human sequences for each non-human FR wherein the sequence identity was higher for individual FR's as compared to complete VH and VL sequences due to the inclusion of the CDRs. Applicant respectfully disagrees with the Examiner's assertion as Cohen et al. do not, in fact, search for the most homologous human sequences based on each FR sequence individually (i.e., FR1, FR2, FR3, and FR4 separately), but rather search the data bases based on FR1, FR2, and FR3 together. At column 5, line 31, when Cohen et al. refer to (3xVH and 3xVL), Cohen et al. are referring to the FR1, FR2 and FR3 sequences together within each V gene of the heavy and light chain variable regions.

Cohen et al. treat FR1, FR2, and FR3 together based on the scientific notion/consensus that the FR1, FR2 and FR3 of a single V gene are inseparable and should only be viewed as a single group when chosen as the framework for grafting CDRs. Cohen et al.'s concept of viewing the FR1, FR2, and FR3 sequences together is in contrast to the present invention which separates and treats independently the FR1, FR2, and FR3 regions. Cohen et al. noted in Column 5, lines 35-37 that, "for the complete VH and VL sequences, identity with the human

sequences were approximately 66% and 60% respectively" because Cohen et al. were comparing sequence homology alongside with the CDRs. Cohen at al., therefore, noted, "the lower percentage of identity when using the complete sequence was due to the hypervariable CDR regions." When the CDRs of a single V region (3xVH or 3xVL) were not considered, "the percent identity for the individual framework regions was higher, ranging from 70-100% and with an average of about 80%" (Column 5, lines 39-41).

Cohen et al., after disregarding the sequence comparison between CDRs, only compared the homology of the "individual framework regions" to the human framework regions from the same antibody. For example, for the 3xVH framework sequence of a particular mouse V region, if the FR1, for example, is 70% homologous to the human sequence, the FR2 is 100% homologous, and the FR3 is 70% homologous, then the overall homology would be 80%. Cohen et al.'s view that FR1, FR2, and FR3 should be treated as a single unit for humanization purpose is illustrated by Cohen et al.'s statement that "the murine antibody used JH4 and JK2. These are most homologous to human JH6 and JK4" (Column 5, lines 41-43). This statement demonstrates that Cohen et al. are viewing FR1, FR2, and FR3 as a single unit and FR4 as a single unit.

Cohen et al. do not disclose or suggest viewing each FR1, FR2, and FR3 separately and independently in choosing framework sequences, potentially from different immunoglobulins chains because Cohen et al. was mimicking the natural recombination in forming the variable region through V gene-J gene joining. One of skill in the art would understand that FR4 resides in the J gene, and there are about 5 J genes available for human, whereas

there are hundreds of V genes for the heavy and light chain immunoglobulin. It is obvious for those skilled in the art to contemplate mimicking the natural VJ or VDJ recombination by assorting J (FR4) sequences, but will find it inconceivable under normal scientific senses that sequences within the V gene (FR1, FR2, and FR3) can be freely assorted and result in a functional protein with reduced immunogenicity.

Furthermore, the Examiner asserts that Benhar et al. teach a rapid method of producing a humanized antibody by FR-patching wherein the parental FR residues that differ from human FR residues are mutated to human residues to encode a human FR and the 4 amino acids immediately adjacent to the CDRs are identical to the parental FR residues. Benhar et al. do not disclose or suggest the framework patching method of the present invention as there is no disclosure or suggestion of choosing <u>different</u> FR residues from potentially different immunoglobulins to replace the parent FR sequences.

Instead, the "framework exchange" technique used by Benhar et al. refers to another technical method for doing CDR grafting (or a different name for describing CDR grafting). For simplicity of illustration, only the heavy chain is discussed. According to Benhar et al., if CDR grafting was adopted, the human 56P1'CL heavy chain framework (FR1, FR2, FR3 and FR4) would be chosen, the murine B3 VH CDRs would then be grafted onto the selected human framework. The murine residues at positions 3, 19, 82b, and 89 would then be back-mutated onto the human framework to maintain binding affinity. The final humanized B3 VH would contain the human 56P1'CL framework,

murine B3 VH CDRs and murine residues at positions 3, 19, 82b, and 89.

Framework exchange is exactly the same concept as above using a different procedure. The so-called "framework exchange" described in Benhar et al. started with comparing the murine B3 VH sequence (i.e., FR1, FR2, FR3, and FR4 together) with the most homologous human VH sequence. In this case, it is human 56P1'CL. Because the framework sequences between murine and human are highly homologous, the authors had identified 14 sequence differences between the human and murine sequences in residues 3, 11, 16, 19, 40, 42, 44, 74, 75, 82a, 82b, 83, 84, and 89. So, if all these framework residues in the murine VH were converted/exchanged into human residues, the framework is the same as the human 56P1'CL. However, Benhar et al. also identified murine residues at positions 3, 19, 82b and 89 to be important for binding, and, therefore, chose to convert only ten residues at positions 11, 16, 40, 42, 44, 74, 75, 82a, 83, and 84 into human residues. The final humanized B3 VH contained the human 56P1'CL framework, murine B3 VH CDRs and murine residues at positions 3, 19, 82b, and 89. This is exemplified at p.12053 of the article in the Results/CDR Grafting section, and in Figure 3. This is just another way of doing humanization as described in Queen et al. Therefore, Benhar et al. describe a humanized antibody in which the human sequences are all derived from a single human immunoglobulin chain. Benhar et al. do not teach a framework-patched immunoglobulin wherein not all of the replaced FR1, FR2, and FR3 of the re-engineered heavy (or light) chain are from the same framework of a single immunoglobulin heavy (or light) chain, as recited in the pending claims.

Therefore, the present invention would not be prima facie obvious over Queen at al. in view of Cohen at al. and Benhar et al. as these references, either alone or in combination, fail to disclose or suggest the framework-patched immunoglobulins disclosed in the present application.

Furthermore, the combination of Queen with Cohen and Benhar provides no reasonable expectation of success when practicing the claimed invention. The combined references teach that the framework regions of an antibody should be replaced as a unit corresponding to that found in existing V genes and J genes. The combined teachings of the cited references would not predict that individual framework regions from different genes could be recombined with a reasonable expectation that the resulting antigen binding affinity would remain within 3-fold of the parent antibody. For this reason also, the cited references fail to provide a prima facie case of obviousness.

In conclusion, the cited references do not render the present invention obvious, and Applicant respectfully requests that this rejection be withdrawn.

Rejection under double patenting

In response to Action Items 14 to 15 on pages 15 to 18 of the Office Action, Applicant will consider filing a terminal disclaimer on a later date in order to overcome the rejection.

CONCLUSION

Applicant believes that the amendments made in the abstract, claims and disclosure, and the arguments put forward hereinabove adequately address the Examiner's concerns. Accordingly, Applicant respectfully requests the Examiner to reconsider and withdraw all previous grounds of objection and rejection, and thereby put this application in conditions for allowance.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, Applicant's undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the FIVE HUNDRED AND TEN DOLLARS ($510.00), for the petition for the three-month extension of time is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-1891. Conversely, authorization is also hereby given to credit the amount of any overpayment to Deposit Account No. 50-1891.

Respectfully submitted,

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I hereby certify that this paper is being deposited this date with the U.S. Postal Service with sufficient postage for first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Albert Wai Kit Chan /SKL 9/25/06
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